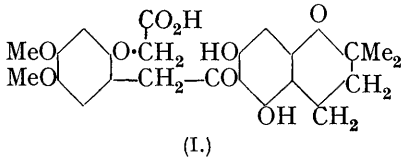
57. *Experiments on the Synthesis of Rotenone and its Derivatives. Part XII. The 2 : 2-Dimethyl-Δ³-chromen Residue of Toxicarol.*

By Walter Bridge, Reginald G. Heyes, and Alexander Robertson.

In Part V (J., 1935, 681) the structure of *apo-* and of dehydro*apo*-toxicarol was clearly demonstrated and the view was expressed that toxicarol and certain of its derivatives contain a 2 : 2-dimethyl-Δ³-chromen nucleus involving the phloroglucinol residue, analogous to that obtaining in deguelin and tephrosin (Part II, J., 1932, 1380). This suggestion was based mainly on the production of acetone from toxicarol and deguelin by hydrolytic fission, in conjunction with the fact that, compared with toxicarol, coumarones and coumarans, *e.g.*, tubanol and *iso*tubanol, are relatively stable to hot aqueous sodium hydroxide, and before directing attention to the remaining experimental details required for the complete structure of toxicarol it was considered essential that clear evidence of the presence of the chromen residue should be obtained. In the first instance the oxidation of *O*-acetyldihydrodehydrotoxicarol was studied because it appeared reasonable to expect that, if toxicarol contained the 2 : 2-dimethyl-Δ³-chromen system, it would probably give rise to an acid analogous to tephrosindicarboxylic acid (Part II, *loc. cit.*). Efforts in this direction, however, have been entirely unsuccessful; *e.g.*, the oxidation of the acetate of dehydrotoxicarol in acetone with aqueous potassium permanganate gave, in addition to 2-hydroxy-4 : 5-dimethoxybenzoic acid and rissic acid, a neutral product (an acetate), m. p. 149°, which did not appear to be suitable for further step-wise degradation. Consequently we turned our attention to the hydrolytic fission of dehydrotoxicarol and of dihydrotoxicarolic acid, having as our objective the isolation of phenols analogous to tubanol and dihydrotubanol.

Degradation of dehydrotoxicarol with warm aqueous sodium hydroxide under a variety of conditions failed to give the expected product, but scission of dihydrotoxicarolic acid with hot 50% reagent yielded a crystalline dihydric phenol, $C_{11}H_{14}O_3$, which behaved as a saturated compound in the presence of hydrogen and a palladium–charcoal catalyst, formed a *diacetate* insoluble in cold aqueous sodium hydroxide, did not contain a carbonyl group, and appeared to have one ethereal oxygen atom. On the basis of the 2 : 2-dimethyl-Δ³-chromen hypothesis and the fact that toxicarol has been shown to contain a phloroglucinol residue this substance was considered likely to be 5 : 7-*dihydroxy*-2 : 2-*dimethylchroman* (II); the properties of the phenol appeared to exclude a structure of the type (III) and from the arguments presented in Part V (*loc. cit.*) the dihydrofuran structure (IV) was considered improbable. That the compound has formula (II) is conclusively established by the fact that it was found to be identical with authentic 5 : 7-dihydroxy-2 : 2-dimethylchroman obtained in excellent yield by the application of Clemmensen's method of reduction to 5 : 7-*dihydroxy*-2 : 2-*dimethylchromanone* (VI, R = H).



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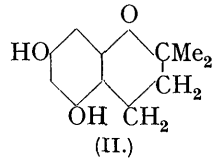

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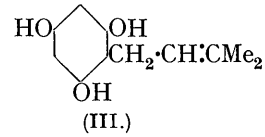
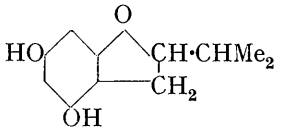


(III.)

Although the condensation of phloroglucinol and ββ-dimethylacryl chloride with the aid of aluminium chloride gives a good yield of the chromanone (VI, R = H), the reaction does not afford conclusive evidence regarding the structure of the product and, since the standard chromanone synthesis (Robinson and co-workers, J., 1926, 945) is inapplicable,

the structure of the compound has been deduced indirectly. It behaves as a saturated substance towards hydrogen in the presence of a palladium catalyst and forms a 2 : 4-*dinitrophenylhydrazone* and a *dimethyl ether* (VI, R = Me) which is insoluble in cold aqueous sodium hydroxide and does not give a ferric reaction, properties sufficing to distinguish the chromanone from the isomeric compounds (V), (VII), and (VIII) but not from the β-*coumaranone* (XII, R = H), all of which could conceivably have been formed by the Friedel–Crafts reaction. Although under certain conditions the chromanone is accompanied by small amounts of a by-product, no trace of an isomeric compound has been observed. The by-product, which has not yet been obtained analytically pure, appears to have the formula $C_{16}H_{18}O_5$, as it gives a *mono*-2 : 4-*dinitrophenylhydrazone* agreeing with this composition and is in all probability of the type (IX).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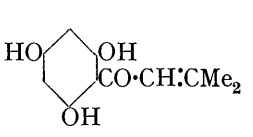
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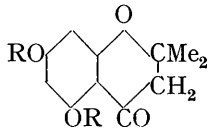
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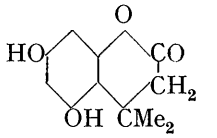
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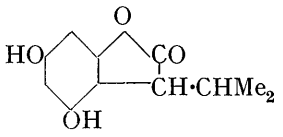
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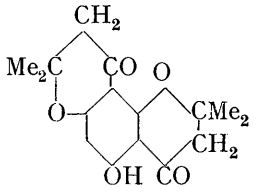
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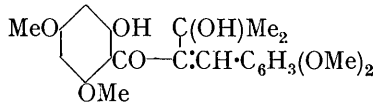
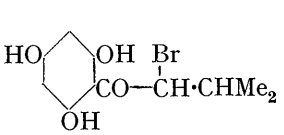

(X.)

On general grounds it is almost certain that the formation of the chromanone (VI, R = H) would proceed by way of the unsaturated ketone (V), a mechanism which is strictly analogous to that obtaining in the synthesis of flavanones by the condensation of cinnamoyl chlorides with *m*-dihydroxyphenols. Nevertheless cyclisation of the ketone (V) could obviously have taken the alternative route with the formation of the coumaranone (XII, R = H) and hence it was essential that clear proof of the chromanone structure of the product should be obtained. For this purpose evidence of the presence of the group $CO{\cdot}CH_2$ in the dimethyl ether of the chromanone would have been conclusive, but our efforts to demonstrate this by standard methods were unsuccessful. Condensation of the dimethyl ether with veratraldehyde in alcoholic sodium hydroxide led to the formation of a compound, m.p. 152·5—153°, which, from appearance (yellow colour) and crimson-red coloration with concentrated sulphuric acid, appeared to be a benzylidene derivative of the chromanone, but which unexpectedly gave a dark red coloration with alcoholic ferric chloride. Analysis indicated the presence of a molecule of water more than that required for 5 : 7-dimethoxy-2 : 2-dimethyl-3-veratrylidenechromanone and hence it would seem that this compound is the styryl derivative (X). This is supported by the fact that when a solution of the chromanone dimethyl ether in 5% alcoholic potassium hydroxide is kept for 24 hours at room temperature the product obtained on acidification has the properties of an *o*-hydroxyphenyl ketone. On the other hand attempts to form a veratrylidene derivative by the standard hydrogen chloride–acetic acid method led to the isolation of an almost colourless, amorphous product which could not be purified and may have contained a bis-derivative of the aldehyde. Similarly, condensation of the dimethyl ether with 2-hydroxy-4-methoxybenzaldehyde in ethyl acetate by means of hydrogen chloride in the usual manner yielded a red chromenopyrylium-like product which has not yet been obtained pure. Efforts to prepare an *iso*nitroso-derivative of the dimethyl ether by the usual method were equally unsuccessful; a compound, m. p. 124—125°, was invariably obtained in small yield, which, however, did not contain nitrogen and was accompanied by a considerable amount of impurities giving a ferric reaction.

Since these attempts to obtain decisive evidence for the chromanone structure proposed for the Friedel–Crafts product (VI, R = H) and its dimethyl ether (VI, R = Me) were unpro-

ductive, the synthesis of the isomeric β-*coumaranone* (XII, R = H) was next investigated. In contrast to the formation of the chromanone (VI, R = H) the condensation of phloro-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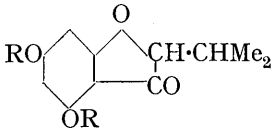
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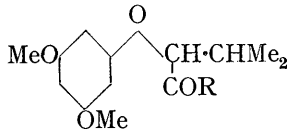

(XIII.)

glucinol with α-bromo*iso*valeryl chloride in nitrobenzene by the Friedel–Crafts method furnished, along with traces of a bromo-compound, a small yield of a product which appeared to be (XII, R = H). This compound behaves as a saturated substance towards hydrogen in the presence of a palladium or platinum catalyst, but, unlike the isomeride (VI, R = H), does not appear to form a 2 : 4-dinitrophenylhydrazone readily and on reduction by Clemmensen's method gives, in addition to much amorphous material, only traces of a phenolic compound. By the methyl iodide–potassium carbonate method an alkali-insoluble methylation product was obtained which could not be satisfactorily purified from more highly methylated by-products (probably trimethyl ether of enolic form of coumaranone) but appeared to consist mainly of the dimethyl ether (XII, R = Me) since it gave rise to a good yield of a 2 : 4-*dinitrophenylhydrazone*, subsequently found to be identical with the 2 : 4-dinitrophenylhydrazone of authentic 4 : 6-dimethoxy-2-*iso*propyl-3-coumaranone (XII, R = Me). The latter compound was prepared by an unambiguous method and hence the β-coumaranone structure of (XII, R = H) is established. Further, since comparison of the 2 : 4-dinitrophenylhydrazones of the β-coumaranone (XII, R = Me) and of the chromanone dimethyl ether (VI, R = Me) showed that the two compounds were isomeric and not identical, therefore the chromanone structure assigned to the latter ether and the parent dihydroxy-compound (VI, R = H) is confirmed. The analogous formation of 7-hydroxy-2 : 2-dimethylchromanone and of 6-hydroxy-2-*iso*propyl-3-coumaranone from resorcinol and the appropriate acid chlorides has also been established (compare Arima and Okamoto, *J. Chem. Soc. Japan*, 1929, **50**, 344), thus affording collateral evidence for the structures herein assigned to the phloroglucinol derivatives. These results will be described in a subsequent communication.

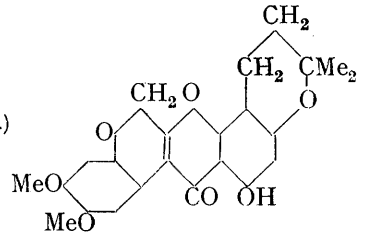
In view of the established formation of the chromanone (VI, R = H) when ββ-dimethylacryl chloride is employed in the Friedel–Crafts reaction the β-coumaranone (XII, R = H) must arise from the intermediate α-bromo-ketone (XI) by direct loss of hydrogen bromide without the formation of an unsaturated ketone (V). This cyclisation may well occur during the process of steam-distillation necessarily employed in working up the reaction mixture.

The authentic coumaranone (XII, R = Me) was prepared according to a standard procedure (Stephen and co-workers, J., 1936, 896) : Interaction of the sodium derivative of phloroglucinol dimethyl ether and ethyl α-bromo*iso*valerate gave rise to a satisfactory yield of the ester (XIII, R = OEt), readily hydrolysed to the acid (XIII, R = OH). Cyclisation of the acid chloride (XIII, R = Cl) in benzene with aluminium chloride furnished a product from which the coumaranone (XII, R = Me) was obtained as a viscous oil, conveniently characterised by the formation of a 2 : 4-dinitrophenylhydrazone.

Although the chromanone structure of 5 : 7-dihydroxy-2 : 2-dimethylchromanone (VI, R = H) normally implies that the reduction product is the chroman (II), the ease of opening of the chromanone ring system (VI, R = Me) under certain conditions (see also experimental section) led us to consider the possibility that, on application of the Clemmensen reaction to (VI, R = H), reduction might be preceded by ring scission to give (V), resulting in the formation of (III), which could then undergo cyclisation to give the dihydrofuran (IV). The evidence at our disposal, however, appears to exclude this mechanism; *e.g.*, by analogy with unsubstituted chromanones and flavanones a ring system of the type (VI) would not be expected to open readily in the presence of acidic reagents; reduction of the chromanone appears to proceed normally, giving an excellent yield of (II) [compare β-coumaranone (XII, R = H)]. In any case, even if the reduction of the chromanone (VI, R = H) did take place by way of the intermediate (III), there is substantial evidence that compounds

of the latter type cyclise to chroman and not coumaran systems, *e.g.*, formation of β-dihydrorotenone and its relationship to deguelin and tephrosin (Part II, J., 1932, 1384; conversion of coumarins into chromanols and chromens, Heilbron and Hill, J., 1927, 2005). Attempts to obtain independent evidence on this question by oxidation of the chroman (II) have so far been unsuccessful.

(XIV.)

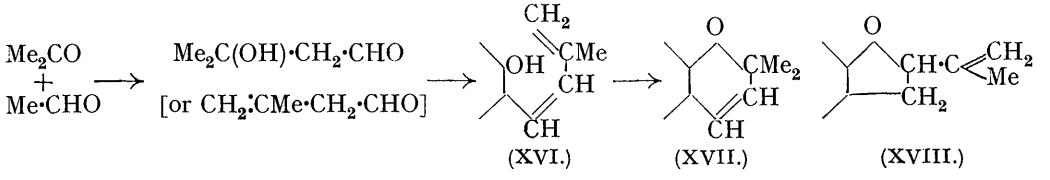


(XV.)

The isolation of the chroman (II) together with the structures established for *apo*- and dehydro*apo*-toxicarol in Part V (*loc. cit.*) affords substantial proof that dihydrotoxicarolic acid is represented by formula (I) and that dehydrodihydrotoxicarol has formula (XIV) or (XV). Further, since the ethylenic linkage of toxicarol is known to be present in the C_5 residue lost in the formation of *apo*toxicarol, it is now clear that toxicarol contains a 2 : 2-dimethyl-Δ^3-chromen residue and hence the alternative structures suggested for toxicarol, dehydrotoxicarol, and for dihydrotoxicarol in Part V are substantiated.

Formation of Acetone from 2 : 2-Dimethyl-Δ^3-chromens.—The formation of acetone by hydrolytic fission appears to be a general property of certain natural 2 : 2-dimethyl-Δ^3-chromens, deguelin, toxicarol, xanthoxyletin and xanthyletin (Part V, *loc. cit.*; J., 1936, 627, 1828) and in these cases this type of scission takes place much more readily than in the case of analogous compounds substituted in the 4-position; thus we have observed that the formation of acetone could not be detected when 7-hydroxy-2 : 2 : 4-trimethyl-Δ^3-chromen was boiled with 50% aqueous sodium hydroxide for 3 hours. Under the experimental conditions employed for the hydrolysis of the natural chromens (*loc. cit.*) it is extremely unlikely that the formation of acetone arises by fission across the double bond, *i.e.*, between the 3- and the 4-C atom of the chromen system, as a first step. This route would doubtless lead to the production of α-hydroxy*iso*butyric acid as an intermediate stage and, although this compound is stated to give acetone on fusion with solid sodium hydroxide, it is stable under conditions considerably more drastic than those necessary for the fission of the Δ^3-chromen systems of the aforementioned natural compounds.

In view of the occurrence of members of the rotenone series—rotenone, deguelin, tephrosin, and toxicarol—in the same or closely related plant species, and of the fact that these compounds contain the C_5 unit, $\overset{C}{C}\!>\!C\text{—}C\text{—}C$, embodied either in a 2 : 2-dimethyl-Δ^3-chromen (type XVII) or in an isomeric coumaran system (type XVIII) it is reasonable to assume that both structures originate from a common type of intermediate, *e.g.* (XVI). On the further assumption that the attachment of the C_5 residue is one of the end processes in the phytochemical production of these compounds we may express the formation of the intermediate type (XVI) thus:



(XVI.) (XVII.) (XVIII.)

The substance (XVI) could then undergo cyclisation in two ways, forming either the chromen (XVII) or the dihydrocoumarone (XVIII). Reversal of this scheme offers a feasible mechanism for the production of acetone by hydrolytic fission of 2 : 2-dimethyl-Δ^3-chromens, unsubstituted in the 3- and 4-positions, analogous to that suggested by Heilbron and Hill (*loc. cit.*) for the decomposition of 2 : 2-diphenyl-4-methyl-Δ^3-chromens, the final stage of

which represents the reversal of an aldol condensation. This mechanism, as indicated by these authors, finds a close analogy in the fission of certain coumarins discovered by Baker (J., 1925, **127**, 2349); *e.g.*, 7-hydroxy-3-phenyl-4-methylcoumarin gives mainly resorcinol and benzyl methyl ketone, which must arise by way of α-phenylacetoacetic acid.

Experimental.

Oxidation of Dehydrotoxicarol Acetate with Potassium Permanganate.—Treatment of dehydrotoxicarol (2·7 g.) with acetic anhydride (10 c.c.) and pyridine (5 c.c.) on the steam-bath for 2 hours gave the acetate, which formed pale straw-coloured needles or rods, m. p. 231—232°, identical with a specimen obtained by Clark's method (*J. Amer. Chem. Soc.*, 1931, **53**, 2264).

A solution of potassium permanganate (1·87 g.) in water (50 c.c.) was added to a well-stirred mixture of the acetate (1·7 g.) in acetone (750 c.c.) in the course of 1½ hours. Next day the manganese dioxide was recovered by filtration, the greater part of the acetone evaporated in a vacuum, the residual liquor treated with excess of aqueous sodium carbonate, and the insoluble product (A) collected. Acidification of the aqueous filtrate precipitated 2-hydroxy-4 : 5-dimethoxybenzoic acid, which had m. p. 213—214° after repeated crystallisation from aqueous acetone and was identical with a synthetical specimen (J., 1931, 2432). The precipitate of manganese dioxide was extracted with boiling water (20 c.c. × 5), and the combined extracts acidified with hydrochloric acid (Congo-red) and concentrated in a vacuum. After the removal of a small quantity of 2-hydroxy-4 : 5-dimethoxybenzoic acid, the residual liquor on extraction with ether gave a small amount of rissic acid, which formed colourless prisms, m. p. 256°, from methyl alcohol and was identified by comparison with an authentic specimen (J., 1932, 1380).

The aforementioned solid (A) was found to consist of a mixture of unchanged dehydrotoxicarol acetate and a neutral compound (B), from which the latter was extracted by means of warm methyl alcohol. Evaporation of the extracts left (B) as colourless plates contaminated with a small amount of dehydrotoxicarol acetate, which was removed by means of warm benzene (30—35°). Repeated crystallisation of the residue from dilute acetone and then dilute methyl alcohol gave (B) in colourless diamond-shaped plates, m. p. 149° after sintering at 143° (Found in air-dried material : C, 59·4, 59·8, 59·9; H, 5·5, 5·4, 5·5%. Found in a specimen dried in a vacuum at 110° : C, 60·6, 60·7, 60·8; H, 5·3, 5·2, 5·7; OMe, 14·4; CH_3·CO, 10·1%). This compound, which had a negative ferric reaction, was insoluble in aqueous sodium carbonate, but slowly dissolved in 8% aqueous sodium hydroxide. Acidification of the alkaline solution gave an amorphous solid having a green ferric reaction.

Hydrolytic Fission of Dihydrotoxicarolic Acid.—A mixture of the acid (Clark, *J. Amer. Chem. Soc.*, 1932, **54**, 2546) (5 g.) and 50% aqueous potassium hydroxide (20 c.c.) was heated (oil-bath) in nitrogen to 200—205° in the course of 14 minutes and then maintained at this temperature for 10 minutes. A solution of the cooled reaction mixture in water (150 c.c.) was acidified with hydrochloric acid (Congo-red), warmed to about 70°, mixed with charcoal, and filtered (wash charcoal with 70 c.c. of water). After the addition of excess of sodium bicarbonate the filtrate was thoroughly extracted with ether (40 c.c. × 10), and the combined extracts washed with brine, dried, and evaporated, leaving 5 : 7-*dihydroxy*-2 : 2-*dimethylchroman* as a light brown oil which gradually solidified. Crystallisation from benzene and then several times from water (charcoal) gave the compound in colourless hexagonal prisms (1 g.), m. p. 162—163°, readily soluble in ethyl or methyl alcohol, acetone, and ethyl acetate (Found : C, 68·1; H, 7·4. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). In alcohol the ferric reaction is negative and in aqueous solution faint blue.

Acetylated with acetic anhydride (1·5 c.c.) and pyridine (0·5 c.c.) on the steam-bath for ½ hour, the chroman (0·5 g.) gave rise to the *diacetate*, which separated from a little methyl alcohol in colourless prisms, m. p. 86° (Found : C, 64·7; H, 6·7. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%). This derivative is soluble in the usual organic solvents and insoluble in cold aqueous sodium hydroxide.

ββ-*Dimethylacrylic Acid.*—Attempts to prepare this compound according to Dutt's method (*J. Indian Chem. Soc.*, 1924, **1**, 297) were unsuccessful.

A mixture of α-bromo*iso*valeric acid ("Organic Syntheses," XI, p. 20) (40 g.) and quinoline (80 g.) was heated to 140—150° and, when the vigorous reaction had ceased, then maintained at 165—170° for 20 minutes. After the addition of excess of dilute hydrochloric acid to the cooled reaction mixture ββ-dimethylacrylic acid was isolated with ether and purified by distillation in a vacuum; yield, 11·5 g. Crystallised from light petroleum (b. p. 40—60°), it had m. p. 67—68°.

When applied to α-bromo*iso*valeric acid, the method used by Perkin (J., 1896, **69**, 1470) for the preparation of acrylic acid from ethyl α-bromo*iso*valerate gave poor yields of an inferior product.

ββ-Dimethylacryl chloride (11 g.), b. p. 45—48°/12 mm., was prepared by gently warming the acid (12 g.) with thionyl chloride and purified by distillation in a vacuum.

5 : 7-*Dihydroxy*-2 : 2-*dimethylchromanone* (VI, R = H).—Aluminium chloride (15·2 g.) was dissolved in a mixture of nitrobenzene (200 c.c.) and phloroglucinol (16·2 g.) (agitate). ββ-Dimethylacryl chloride (11·5 g.) was then gradually introduced, and the reaction mixture kept at room temperature for 4 days. After the addition of ice (150 g.) and dilute hydrochloric acid (100 c.c.) the product, mixed with nitrobenzene, was isolated with ether, the nitrobenzene was removed by means of steam, and the hot aqueous liquor decanted from brown viscous resin. On being kept, the cooled aqueous solution slowly deposited the *chromanone*; a further quantity was obtained by extraction of the resinous residue with chloroform–light petroleum. Yield of crude material, 14·5 g. Recrystallised from chloroform or dilute alcohol, the compound formed colourless elongated prisms, m. p. 198°, readily soluble in alcohol, acetone or ethyl acetate and sparingly soluble in benzene (Found : C, 63·4; H, 5·7. $C_{11}H_{12}O_4$ requires 63·5; H, 5·8%). With alcoholic ferric chloride it gave a purple coloration.

Excess of 2 : 4-dinitrophenylhydrazine hydrochloride in dilute hydrochloric acid was added to a solution of the chromanone (0·7 g.) in alcohol (20 c.c.), and the mixture warmed for 10 minutes on the water-bath and then kept for 16 hours at room temperature. The resulting 2 : 4-*dinitrophenylhydrazone* formed blood-red needles, m. p. 277—278°, from alcohol (Found : N, 14·3. $C_{17}H_{16}O_7N_4$ requires N, 14·4%).

In the preparation of the chromanone it was found that the proportion of aluminium chloride employed had considerable effect upon the tractability of the product obtained and the foregoing procedure appeared to give an optimum result. In another experiment where phloroglucinol (1·25 mols.), acid chloride (1 mol.), and aluminium chloride (2·5 mols.) were allowed to interact in nitrobenzene for 7 days, the aqueous liquor left on removal of nitrobenzene gave only a small amount of the chromanone, and the resinous product, which did not yield crystalline material with solvents, was dissolved in ether and the solution extracted with aqueous sodium carbonate. In the course of the extraction a small amount of a solid sodium derivative crystallised. Decomposition of this material in a little methyl alcohol with acetic acid gave a compound (IX), which separated from light petroleum (b. p. 80—100°) in colourless elongated prisms, m. p. 134° (the melt becoming clear at 138°), giving a red coloration with alcoholic ferric chloride (Found in material dried at 90° : C, 66·9, 67·0; H, 6·3, 6·3; *M*, 245, 253. Calc. for $C_{16}H_{18}O_5$: C, 66·2; H, 6·2%; *M*, 290). The substance is soluble in alcohol, acetone, chloroform, benzene, or ethyl acetate and on treatment with 2 : 4-dinitrophenylhydrazine hydrochloride (method employed in the case of chromanone) gave rise to a 2 : 4-*dinitrophenylhydrazone*, which formed short red prisms, m. p. 267—268° (Found : C, 56·3; H, 4·9; N, 11·5. $C_{22}H_{22}O_8N_4$ requires C, 56·2; H, 4·7; N, 11·9%).

Acidification of the combined aqueous sodium carbonate extracts gave a further small amount of chromanone, m. p. 198° after purification.

5 : 7-*Dimethoxy*-2 : 2-*dimethylchromanone* (VI, R = Me).—Methylation of 5 : 7-dihydroxy-2 : 2-dimethylchromanone (2 g.) was effected with methyl iodide (4 c.c.) and potassium carbonate (7 g.) in boiling acetone (60 c.c.) in the course of about 7 hours; after 4 hours more iodide (2 c.c.) and more carbonate (3 g.) were added. When a test portion of the reaction mixture did not give a ferric reaction the potassium salts were removed by filtration (wash with excess acetone), the solvent evaporated, and an ethereal solution of the residue washed with dilute aqueous sodium hydroxide, dried, and evaporated. Crystallisation of the residual product from light petroleum (b. p. 60—80°) gave the *dimethyl ether* in colourless plates (1·7 g.), m. p. 104·5—105°, soluble in benzene or alcohol and having a negative ferric reaction [Found : C, 66·1; H, 6·9; OMe, 26·7. $C_{11}H_{10}O_2(OMe)_2$ requires C, 66·1; H, 6·8; OMe, 26·3%].

When a solution of the chromanone (0·4 g.) in alcohol (13 c.c.) was boiled with 2 : 4-dinitrophenylhydrazine hydrochloride (from 0·4 g. of the hydrazine) for 2 minutes, the 2 : 4-*dinitrophenylhydrazone* separated almost immediately; it formed blood-red needles (0·5 g.), m. p. 240°, from ethyl acetate (Found : N, 13·5. $C_{19}H_{20}O_7N_4$ requires N, 13·5%).

The product obtained by treating the chromanone with semicarbazide acetate in the usual manner separated from alcohol in colourless elongated prisms, m. p. 245° (Found : N, 13·7. Calc. for $C_{14}H_{19}O_4N_3$: N, 14·3%. Calc. for $C_{14}H_{19}O_4N_3,H_2O$: N, 14·0%). As this compound possesses the unexpected property of giving a reddish-brown coloration with alcoholic ferric chloride, it is probably the semicarbazone of a hydrated derivative of the chromanone, *i.e.*, of β : 2-dihydroxy-4 : 6-dimethoxy*iso*valerophenone (the semicarbazones of *o*-hydroxypropiophenone and of 3-chloro-2-hydroxyacetophenone give dark brownish-violet ferric reactions). On treatment with hot alcoholic 2 : 4-dinitrophenylhydrazine hydrochloride, however, this derivative was quan-

titatively converted into the 2 : 4-dinitrophenylhydrazone, m. p. 236—237°, which on being mixed with an authentic specimen, m. p. 240°, melted at 238—239°.

5 : 7-*Dihydroxy*-2 : 2-*dimethylchroman* (II).—A solution of 5 : 7-dihydroxy-2 : 2-dimethylchromanone (2 g.) in a mixture of alcohol (20 c.c.), acetic acid (10 c.c.), water (46 c.c.), and concentrated hydrochloric acid (34 c.c.) containing amalgamated zinc dust (Robinson and Shah, J., 1934, 1497) (80 g.) was kept at room temperature for 2 days, treated with 12% hydrochloric acid (20 c.c.), heated on the steam-bath for 1 hour, and then refluxed for 6 hours; more acid (20 c.c.) was added. The hot liquor was decanted, cooled, and extracted several times with ether and the combined extracts were well washed with aqueous sodium bicarbonate, dried, and evaporated, leaving the chroman, which separated from benzene and then water in colourless prisms (1·2 g.), m. p. 162—163°, identical in every way with the natural product (Found : C, 67·9; H, 7·3%). The diacetate formed colourless prisms, m. p. and mixed m. p. 86°, from a small volume of methyl alcohol.

4 : 6-*Dihydroxy*-2-iso*propyl*-3-*coumaranone* (XII, R = H).—α-Bromo*iso*valeryl chloride (18 g.) was slowly added to a cooled solution of phloroglucinol (14 g.) and aluminium chloride (15 g.) in nitrobenzene (200 c.c.), and the mixture kept for 4 days; more aluminium chloride (6 g.) was added after 2 days. The reaction mixture was very slowly heated to 60°, maintained at this temperature for 1 hour, cooled, and treated with excess of ice and hydrochloric acid. The mixture was extracted several times with ether, the combined extracts evaporated, and the nitrobenzene removed from the residue by a current of steam. On being kept, the residual aqueous liquor slowly deposited the *coumaranone* (4·5 g.), which formed colourless rhombic prisms, m. p. 196°, from dilute methyl alcohol, readily soluble in alcohol or ethyl acetate and sparingly soluble in benzene (Found : C, 63·3; H, 5·8. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%). Mixed with 5 : 7-dihydroxy-2 : 2-dimethylchromanone, this compound melted at 170—184°. With alcoholic ferric chloride it gave a purple coloration.

After the separation of the crude coumaranone the aqueous liquor deposited traces of a product containing bromine, m. p. 110—115° after being once recrystallised from water.

4 : 6-*Dimethoxy*-2-iso*propyl*(β)*coumaranone* (XII, R = Me).—(A) Ethyl α-bromo*iso*valerate (20 g.) was gradually added to a solution of phloroglucinol dimethyl ether (20 g.) in alcohol (80 c.c.) containing sodium ethoxide (from 3 g. of sodium) and next day the mixture was gently refluxed for 6 hours. After the removal of the greater part of the alcohol by distillation in a vacuum the residue was diluted with water, the solution extracted several times with ether, and the combined ethereal extracts washed with excess of 1% aqueous sodium hydroxide to remove unchanged phloroglucinol dimethyl ether, and evaporated. The residual mixed esters were hydrolysed with excess of 12% alcoholic sodium hydroxide at room temperature for 16 hours and on isolation in the usual manner the resulting 3 : 5-dimethoxy-α-phenoxy*iso*valeric acid (XIII, R = OH) (7 g.) (fraction, b. p. 160—170°/0·1 mm.) was separated from ββ-dimethylacrylic acid (6 g.) by distillation in a high vacuum and then crystallised from aqueous alcohol, forming colourless prisms, m. p. 92°.

Prepared by means of phosphorus pentachloride (4·4 g.), the acid chloride (from 5 g. of acid) was dissolved in purified benzene (50 c.c.) and then treated with aluminium chloride (2·9 g., added in the course of ½ hour). 3 Hours later, excess of ice and dilute hydrochloric acid was introduced, and the product and benzene isolated with ether. After having been washed with aqueous sodium bicarbonate to remove unchanged acid, the ether–benzene solution was evaporated, and the residue distilled in a high vacuum, giving a main fraction (2 g.). Redistillation of this material gave a clear, very viscous liquid, b. p. 140—150°/0·1 mm., which had the characteristic coumaranone odour and gave rise to a 2 : 4-*dinitrophenylhydrazone*, forming deep red needles, m. p. 185°, from alcohol (Found : N, 13·2. $C_{19}H_{20}O_7N_4$ requires N, 13·5%).

(B) 4 : 6-Dihydroxy-2-*iso*propylcoumaranone (1 g.) was methylated with methyl iodide (6 c.c., added in two portions) and excess of potassium carbonate in boiling acetone for 6 hours; a test sample did not give a ferric reaction. On isolation and removal of phenolic material by means of dilute sodium hydroxide the product was obtained as a viscous oil, which partly solidified and on treatment with hot alcoholic 2 : 4-dinitrophenylhydrazine hydrochloride gave rise to the coumaranone-2 : 4-dinitrophenylhydrazone, m. p. 185°, identical in every way with a specimen obtained by method (A) (Found : N, 13·4%).

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